CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

SIDURON

Chemical Code # 603, Tolerance # 50166

7/30/99

I. DATA GAP STATUS

Chronic toxicity, rat:	No study on file[1]
Chronic toxicity, dog:	Inadequate study; no adverse effects indicated[1]
Oncogenicity, rat:	Inadequate study; **possible adverse effects indicated**[1]
Oncogenicity, mouse:	No study on file[1]
Reproduction, rat:	Inadequate study; no adverse effects indicated[1]
Teratology, rat:	No data gap; no adverse effects
Teratology, rabbit:	No study on file[1]
Gene mutation:	No data gap; no adverse effects
Chromosome effects:	No data gap; no adverse effects
DNA damage:	No data gap; no adverse effects
Neurotoxicity:	No study on file[1]

Toxicology one-liners are attached.

All record numbers through 165097 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T174364
P. Leung, 7/30/99

[1] New active ingredient, siduron, submitted for terrestrial non-food use. These studies are not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

No study submitted.

CHRONIC TOXICITY, RAT

No study submitted.

CHRONIC TOXICITY, DOG

027; 164663; "Long-Term Feeding Tests with 1-(2-Methylcyclohexyl)-3-Phenylurea [INZ-1318; Tupersan; Siduron]"; (Henry Sherman, *et al*, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 201-67; 12/28/67); 831 (dog); IN Z-1318 Wettable Powder (52.6% a.i.) was fed in the diet at concentrations of 0 (3M/3F), 100 (3M/3F), 500 (3M/3F), and 2500 (4M/4F) ppm of a.i. to adult (1-2 year old) beagle dogs for two years; interim sac of 1M/1F at high-dose after one year; no mortalities or treatment-related signs of toxicity; brain weights appeared to be decreased and liver weights appeared to be increased in both males and females, but the small group size and variation in age of the animals makes the data difficult to interpret; **no adverse effects;** the study contains numerous deficiencies including use of formulated product instead of technical grade, no justification for dose selection, no diet analysis, small group size and use of older animals, no ophthalmology, no statistical analysis, and incomplete report; **Unacceptable** and cannot be upgraded. (Duncan, 7/14/99)

ONCOGENICITY, RAT

027; 164663; "Long-Term Feeding Tests with 1-(2-Methylcyclohexyl)-3-Phenylurea [INZ-1318; Tupersan; Siduron]"; (Henry Sherman, *et al*, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 201-67; 12/28/67); 835 (rat); IN Z-1318 Wettable Powder (52.6% a.i.) was fed in the diet at concentrations of 0, 0, 100, 500, and 2500 ppm of a.i. to groups of 36M/36F Crl:CD rats for two years; slightly reduced food consumption and weight gain in high-dose females; no treatment-related signs of toxicity or difference in mortality rates; **possible adverse effects:** increase in thyroid follicular cell hyperplasia and adenomas in males (adenomas: 1/30 at high-dose vs. none in any other group), increase in anterior pituitary adenomas in females (11/27, 12/30, 15/33, 13/29, and 18/28 in control through high-dose); the study contains numerous deficiencies including use of formulated product instead of technical grade; small group size; and lack of diet analysis, serum chemistry measurements, ophthalmological exams, and statistical analyses; **Unacceptable** and cannot be upgraded. (Duncan, 7/9/99)

ONCOGENICITY, MOUSE

No study submitted.

REPRODUCTION, RAT

027; 164663; "Long-Term Feeding Tests with 1-(2-Methylcyclohexyl)-3-Phenylurea [INZ-1318; Tupersan; Siduron]"; (Henry Sherman, *et al*, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 201-67; 12/28/67); 835 (rat); IN Z-1318 Wettable Powder (52.6% a.i.) was fed in the diet to groups of 16M/16F Crl:CD rats at 0, 100, and 500 ppm of a.i. continuously for three F_1 generations, two F_2 generations, and two F_3 generations; no clinical observation, food consumption, or body weight data was reported; pup weight, sex, survival, and

growth data were not reported; dams were apparently not necropsied; **no adverse effects** on fertility, gestation, viability, and lactation indices were observed, and no abnormalities were observed during histological examination of tissues from F_{3B} pups; **Unacceptable** and cannot be upgraded. (Duncan, 7/14/99)

TERATOLOGY, RAT

029, -030; 164670, 164673; "Teratogenicity Study of IN Z1318-70 (Siduron) in the Rat" (Lauren B. Rickard, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 136-89; 8/2/89); 833; IN Z1318-70 (Lot No. A060588-31, 6-88; 99.9%), was dosed an aqueous suspension in 0.5% methyl cellulose to groups of 25 mated female Crl:CD rats at dose levels of 0 (vehicle), 30, 150, 750, and 1500 mg/kg/day on days 7-16 of gestation; signs of maternal toxicity were reduced food consumption and body weight gain during the dosing period (statistically significant, $p \leq 0.05$, in 1500 mg/kg/day dams); no developmental toxicity was observed; mean fetal weight (males, females, and total) was significantly reduced in most dose groups except 150 mg/kg/day, but this finding did not appear to be toxicologically relevant because the magnitude of the decrease was very small and the dose-related trend was weak; **no adverse effects; maternal NOEL = 750 mg/kg/day (based on reduced food consumption and weight gain); developmental NOEL = 1500 mg/kg/day (no toxicologically significant effects); **Acceptable.** (Duncan, 7/7/99)

TERATOLOGY, RABBIT

No study submitted.

GENE MUTATION

031; 164734, 164731; "Mutagenicity Testing of IN Z1318-70 in the *Salmonella typhimurium* Plate Incorporation Assay"; (Vincent L. Reynolds; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 820-88; 1/12/89); IN Z1318-70 (Lot No. A060588-31, 6-88; 99.9%), dissolved in DMSO; *S. typhimurium* TA97, TA98, TA100, and TA1535 with and without activation (Aroclor 1254-induced rat liver S9 fraction), by plate incorporation; 0 (DMSO), 10, 50, 100, 500, 1000 ug/plate, duplicate plates/treatment, two identical trials; 48 hr incubation; **no adverse effects; no increase in reversion rates; positive controls were functional; **Acceptable.** (Duncan, 6/17/99)

031; 164733, 164730; "Mutagenicity Evaluation of IN Z1318-70 in the CHO/HPRT Assay"; (Karin S. Bentley; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 770-88; 1/26/89); IN Z1318-70 (Lot No. A060588-31, 6-88; 99.9%), dissolved in DMSO; CHO-K1-BH4 cells were exposed to five concentration of the test article (5, 10, 50 ,100, 208.9 ug/ml) in activated (Aroclor 1254-induced male rat liver S9 fraction) and non-activated cultures for 5 h (activated) or 18-19 h (non-activated) followed by a 7-d expression period and 6-8 d for mutant selection, with appropriate vehicle and positive controls; duplicate cultures/dose level; 2 trials; **no adverse effects; no significant increases in mutation frequency were observed; positive controls were functional; **Acceptable.** (Duncan, 6/17/99)

CHROMOSOME EFFECTS

031; 164681, 164732; "*In vitro* Evaluation of IN Z1318-70 for Chromosome Aberrations in Human Lymphocytes"; (Demetra A. Vlachos; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 175-89; 5/12/89); IN Z1318-70 (Lot No. A060588-31, 6-88; purity = 99.9%), dissolved in DMSO; human lymphocytes cultured from a male and female donor were treated with 0 (DMSO), 0.01, 0.06, 0.10, and 0.12 mg/ml for 3 h, with and without activation (Aroclor 1254-induced rat liver S9 fraction); two replicate cultures/dose level were tested with appropriate vehicle and positive (MMC, CP) controls; two trials; 100 metaphases/treatment level were examined; **no adverse effects; no significant increases in frequency of chromosomal

aberrations were observed; positive controls were functional **Acceptable.** (Duncan, 6/17/99)

DNA DAMAGE

031; 164679, 164735; "Assessment of IN Z1318-70 in the *In vitro* Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes"; (Karin S. Bentley; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 53-89; 3/17/89); primary hepatocyte cultures from an adult male Crl:CD BR rat were treated with IN Z1318-70 (Lot No. A060588-31, 6-88; 99.9%), dissolved in DMSO for 18 h at concentrations of 0.1, 0.5, 1, 5, 10, 50, 100, 150, and 208.9 ug/ml (FIRST TRIAL) and 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 50, and 100 ug/ml (SECOND TRIAL) and labeled *in vitro* with ^{3}H-TdR; 25 cells on each of two slides/treatment were counted; **no adverse effects; no increase in net nuclear grain counts at any test concentration; positive control (2-AAF) was functional; **Acceptable.** (Duncan, 6/17/99)

NEUROTOXICITY

No study submitted.

SUBCHRONIC STUDIES

023; 165095; "Ninety-Day Feeding Study with 1-(2-Methylcyclohexyl)-3-Phenylurea [INZ-1318]"; (H. Sherman, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 41-64; 4/7/64); 821; IN Z-1318-13 (N. B. 4831-130; 98%) was fed in the diet at concentrations of 0, 50, 500, and 5000 ppm (increased to 7500 ppm after week 6) to groups of 10M/10F Crl:CD rats for 13 weeks; no deaths or signs of toxicity; slightly reduced total food consumption and total weight gain in high-dose females, slight anemia in high-dose males; **no adverse effects**; the study contains numerous deficiencies including lack of diet analysis, serum chemistry measurements, and ophthalmological exams, and limited histopathology; **Unacceptable** and cannot be upgraded. (Duncan, 6/29/99)

****032, 023; 164736, 165097;** "Repeated Dose Dermal Toxicity: 21-Day Study with IN Z1318-70 in Rabbits"; (William J. Brock, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 165-89; 6/12/89); 822; IN Z1318-70 (Lot No. A060588-31, 6-88; 99.9%) was applied to the skin and moistened with dimethyl phthalate (DMP); 0 (DMP), 50, 350, 1500 mg/kg/day; 5 animals/sex/dose level; doses were applied daily for 21-22 days; 6-hour/day exposure, occlusive wrap; no mortality or signs of toxicity; minimal to mild dermal irritation in all treated groups; **adverse effects:** absolute and relative testes weights were decreased in treated males; testes/body weights were 72%, 64%, and 56% of the control value for the low-, mid-, and high-dose groups, respectively; associated histological findings consisted of germinal maturation arrest in the testes, and atrophy of the epididymides and prostate/proprostate; a systemic NOEL was not established in males; systemic NOEL (F) = 1500 mg/kg/day (no effects at HDT); Dermal NOEL (M/F) < 50 mg/kg/day (based on subacute inflammation of superficial dermis); **Acceptable**. (Duncan, 6/17/99)

033; 164737; "Repeated Dose Dermal Toxicity: 21-Day Study with IN Z1318-70 (Siduron) in Male Rabbits"; (Dolores E. Malek, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 108-91; 10/24/91); 822; IN Z1318-70 (Lot No. A060588-31, 6-88; 99.9%) was applied to the skin and moistened with dimethyl phthalate (DMP); 0 (DMP), 5, 15, 25, 50, 1500 mg/kg/day; 10 peripubertal and 10 adult males/dose level (except p-p controls=9 males); 21 daily doses; 6-hour/day exposure, occlusive wrap; half of each group was terminated at the end of the dosing period, half after 21-d recovery; no mortality or signs of toxicity, except dermal irritation; no discernable effect on serum testosterone levels; no adverse effects; Systemic NOEL (M) = 1500 mg/kg (no effect at HDT); Dermal NOEL (M) < 5 mg/kg (dermal irritation). **Supplemental.** (Duncan, 6/24/99)

023; 165096; "Repeated Dose Dermal Toxicity: 21-Day Study with IN Z1318-70 (Siduron) in Male

Rabbits (Testicular Maturation in Prepubertal New Zealand White Rabbits)"; (S. R. Frame, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Lab Report No. 108-91 SUPP 1; 1/11/93; 822; five groups of 15 male NZW rabbits of identical age were maintained without treatment and killed at ages 13, 14, 15, 16, or 17 weeks; body, testes, epididymides, and accessory sex organ weights were measured at termination, and an assessment of sexual maturity was made by examining testicular histology; results showed that testicular weights and testicular maturity were strongly correlated to one another, within age groups and independent of age, but neither were strongly correlated to body weight; testicular weights and testicular maturity were markedly variable in all age groups, but particularly at 14 wks. **Supplemental.** (Duncan, 6/30/99)

METABOLISM STUDIES

Metabolism, Rat

028; 164667; "Metabolic Fate of Siduron in the Animal"; (I. J. Belasco, *et al*, *Agricultural and Food Chemistry*, Vol. 17, No. 5, Sept./Oct. 1969, pp. 1000-1003); 851; urine from a dog receiving 2500 ppm siduron in the diet was collected and analyzed for the parent compound and metabolites using a colorimetric method, and mass, IR, and NMR spectrometry, and a metabolic pathway was proposed; none of the parent compound was found, but three glucuronide conjugates of hydroxy-substituted siduron were isolated and identified, one substituted on the phenyl ring, one substituted on the cyclohexyl ring, and another substituted in both locations; it appears that siduron is first hydroxylated at either location, then both of these mono-hydroxylated compounds are hydroxylated again to form 1-(4-hydroxy-2-methylcyclo-hexyl)-3-*p*-hydroxyphenylurea; comparison of urine from the dog with that from a rat on a similar 2500 ppm diet, showed that the rat formed slightly less of the cyclohexyl-substituted compound than the dog; 800-1000 ppm of total siduron metabolites was found in the urine of these two animals. **Supplemental.** (Duncan, 7/14/99)